```
      (FILE 'HOME' ENTERED AT 08:08:40 ON 13 AUG 1998)

      INDEX 'AGRICOLA, AIDSLINE, ANABSTR, AQUASCI, BIOBUSINESS, BIOSIS,
      BIOTECHABS, BIOTECHDS, CABA, CANCERLIT, CAPLUS, CEABA, CEN, CIN,
      CJACS, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
      DRUGLAUNCH, DRUGNL, DRUGU, EMBAL, EMBASE, FSTA, GENBANK, ...'
      ENTERED AT 08:09:33 ON 13 AUG 1998
                 SEA LIPSTATIN AND OBESITY
                ---------
                3    FILE BIOTECHABS
                3    FILE BIOTECHDS
                3    FILE CAPLUS
                1    FILE CIN
                1    FILE CJACS
                2    FILE EMBASE
                1    FILE MEDLINE
                1    FILE PHIN
                2    FILE PROMT
                4    FILE SCISEARCH
                1    FILE TOXLINE
                1    FILE TOXLIT
                2    FILE USPATFULL
                1    FILE WPIDS
                1    FILE WPINDEX
L1               QUE LIPSTATIN AND OBESITY
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      FILE 'SCISEARCH, BIOTECHDS, CAPLUS, EMBASE, PROMT, USPATFULL, CIN,
      CJACS, MEDLINE, PHIN, TOXLINE, TOXLIT, WPIDS' ENTERED AT 08:10:16
      ON 13 AUG 1998
L2            23 S LIPSTATIN AND OBESITY
L3            16 DUP REM L2 (7 DUPLICATES REMOVED)

      FILE 'USPATFULL' ENTERED AT 08:21:46 ON 13 AUG 1998

      INDEX 'AGRICOLA, AIDSLINE, ANABSTR, AQUASCI, BIOBUSINESS, BIOSIS,
      BIOTECHABS, BIOTECHDS, CABA, CANCERLIT, CAPLUS, CEABA, CEN, CIN,
      CJACS, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
      DRUGLAUNCH, DRUGNL, DRUGU, EMBAL, EMBASE, FSTA, GENBANK, ...'
      ENTERED AT 08:21:58 ON 13 AUG 1998
                 SEA LIPASE(15W)INHIBIT? AND ANTIBOD?
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                 1    FILE AGRICOLA
                 1    FILE ANABSTR
                83    FILE BIOSIS
                 0*   FILE BIOTECHABS
                 3    FILE BIOTECHDS
                 8    FILE CABA
                 9    FILE CANCERLIT
                76    FILE CAPLUS
                11    FILE CJACS
                 3    FILE DISSABS
                 3    FILE DRUGU
                56    FILE EMBASE
                 1    FILE FSTA
                 4    FILE IFIPAT
                 5    FILE JICST-EPLUS
                 9    FILE LIFESCI
                60    FILE MEDLINE
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                2   FILE PHIN
                2   FILE PROMT
               32   FILE SCISEARCH
                4   FILE TOXLINE
                9   FILE TOXLIT
               63   FILE USPATFULL
                7   FILE WPIDS
                0*  FILE WPINDEX
L4               QUE LIPASE(15W) INHIBIT? AND ANTIBOD?
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     FILE 'BIOSIS, CAPLUS, USPATFULL, MEDLINE, EMBASE, SCISEARCH, CJACS,
     CANCERLIT, LIFESCI, TOXLIT, CABA, WPIDS, JICST-EPLUS, IFIPAT,
     TOXLINE, BIOTECHDS, DISSABS, DRUGU, PHIN, PROMT, AGRICOLA, ANABSTR,
     FSTA' ENTERED AT 08:30:38 ON 13 AUG 1998
L5             856 S LIPASE(15W)ANTIBOD?
L6               4 S L5 AND OBESITY
L7               4 DUP REM L6 (0 DUPLICATES REMOVED)
L8             190 S L5 AND (TREAT? OR THERAPY)
L9              89 DUP REM L8 (101 DUPLICATES REMOVED)
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Mode of action of orlistat.

AU Guerciolini R.
CS R. Guerciolini, Div. International Clinical Research, Hoffmann-La Roche Inc., Nutley, NJ, United States

SO International Journal of Obesity, (1997) 21/SUPPL. 3 (S12-S23).
Refs: 42
ISSN: 0307-0565 CODEN: IJOBDP
CY United Kingdom
DT Journal
FS 030 Pharmacology
039 Pharmacy
037 Drug Literature Index
LA English
SL English

AB Gastric and pancreatic lipases are enzymes that play a pivotal role in the digestion of dietary fat. Orlistat, a semisynthetic derivative of **lipstatin**, is a potent and selective inhibitor of these enzymes, with little or no activity against amylase, trypsin, chymotrypsin and phospholipases. It exerts its effect within the gastrointestinal (GI) tract. Orlistat acts by binding covalently to the serine residue of the active site of gastric and pancreatic lipases. When administered with fat-containing foods, orlistat partially inhibits hydrolysis of triglycerides, thus reducing the subsequent absorption of monoacylglycerides and free fatty acids. This effect can be measured using 24 h faecal fat excretion as a representative pharmacodynamic parameter. Orlistat's pharmacological activity is dose-dependent and can be described by a simple E(max) model which exhibits an initial steep portion of the dose-response curve with a subsequent plateau (.apprx. 35% inhibition of dietary fat absorption) for doses above 400 mg/d. At therapeutic doses (120 mg tid with main meals) administered in conjunction with a well balanced, mildly hypocaloric diet, the inhibition of fat absorption (.apprx. 30% of ingested fat) contributes to an additional caloric deficit of approximately 200 calories. Orlistat does not produce significant disturbances to GI physiological processes (gastric emptying and acidity, gallbladder motility, bile composition and lithogenicity) or to the systemic balance of minerals and electrolytes. Similarly, orlistat does not affect the absorption and pharmacokinetics of drugs with a narrow therapeutic index (phenytoin, warfarin, digoxin) or compounds frequently used by obese patients (oral contraceptives, glyburide, pravastatin, slow-release nifedipine).

L3 ANSWER 15 OF 16 BIOTECHDS COPYRIGHT 1998 DERWENT INFORMATION LTD
AN 86-10072 BIOTECHDS
TI Leucine derivatives;
lipstatin or tetrahydolipstatin preparation using Streptomyces toxytricini; hypolipemic and anorectic lipase-inhibitor
PA Roche
PI US 4598089 1 Jul 1986
AI US 84-621827 18 Jun 1984
PRAI CH 83-3415 22 Jun 1983
DT Patent
LA English
OS WPI: 85-007713 [02]
AB Novel leucine derivatives include **lipstatin** (Ia) and tetrahydrolipstatin. They show pancreas lipase-inhibitor activity and can be used for the control or prevention of **obesity** and hyperlipemia. **Lipstatin** is obtained by cultivation of Streptomyces toxytricini 85-13 (NRRL 15443). Cultivation is performed in a medium containing C- and N-source plus inorganic salts at 20-37 deg for 1-6 days. **Lipstatin** is recovered by conventional methods. For example, the cell mass is extracted with methanol and ethanol, while the culture supernatant is extracted with methylene chloride or ethyl acetate. The material produced from the extracts is subjected to multiplicative extraction with the system hexane-methanol-water (50:40:9), filtration chromatography over silica gel eluting with hexane or ethyl acetate, and chromatography on apolar carriers, eluting with polar solvents. Tetrahydrolipstatin is obtained from **lipstatin** by hydrogenation. (8pp)